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Weber et al.

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(54) **METHOD FOR SPRAY-COATING A MEDICAL DEVICE HAVING A TUBULAR WALL SUCH AS A STENT**

(58) **Field of Search** ..... 427/2.1, 2.24,  
427/2.25, 2.28, 457, 458, 466, 472, 471,  
476

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(73) **Assignee:** Boston Scientific SciMed, Inc., Maple Grove, MN (US)

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(\*) **Notice:** Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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(57) **ABSTRACT**

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(22) **Filed:** Mar. 24, 2004

(65) **Prior Publication Data**

US 2004/0185168 A1 Sep. 23, 2004

#### Related U.S. Application Data

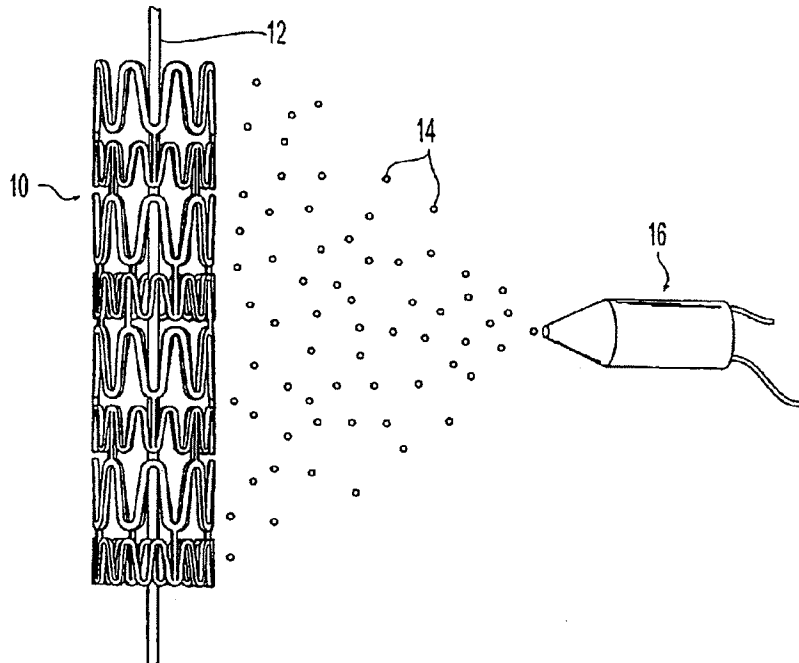
(63) Continuation of application No. 10/109,073, filed on Mar. 28, 2002, now Pat. No. 6,743,463.

(51) **Int. Cl.<sup>7</sup>** ..... A16L 27/00

(52) **U.S. Cl.** ..... 427/2.24; 427/2.1; 427/2.25;  
427/2.28; 427/457; 427/458; 427/466; 427/471;  
427/472; 427/476

A method for electrostatic spray-coating a medical device having a tubular wall, such as a stent, having an inner surface, an outer surface and openings therein. The tubular wall is grounded or electrically charged, and an electrically charged conductive core wire is located axially through the center of the stent. An electrical potential is applied to the conductive core wire to impart an electrical charge to the conductive core wire. The tubular wall is exposed to an electrically charged coating formulation, and the electrically charged coating formulation is deposited onto a portion of the tubular wall to form a coating. The electrical potentials of the conductive core wire and tubular wall can be repeatedly alternated.

**32 Claims, 4 Drawing Sheets**

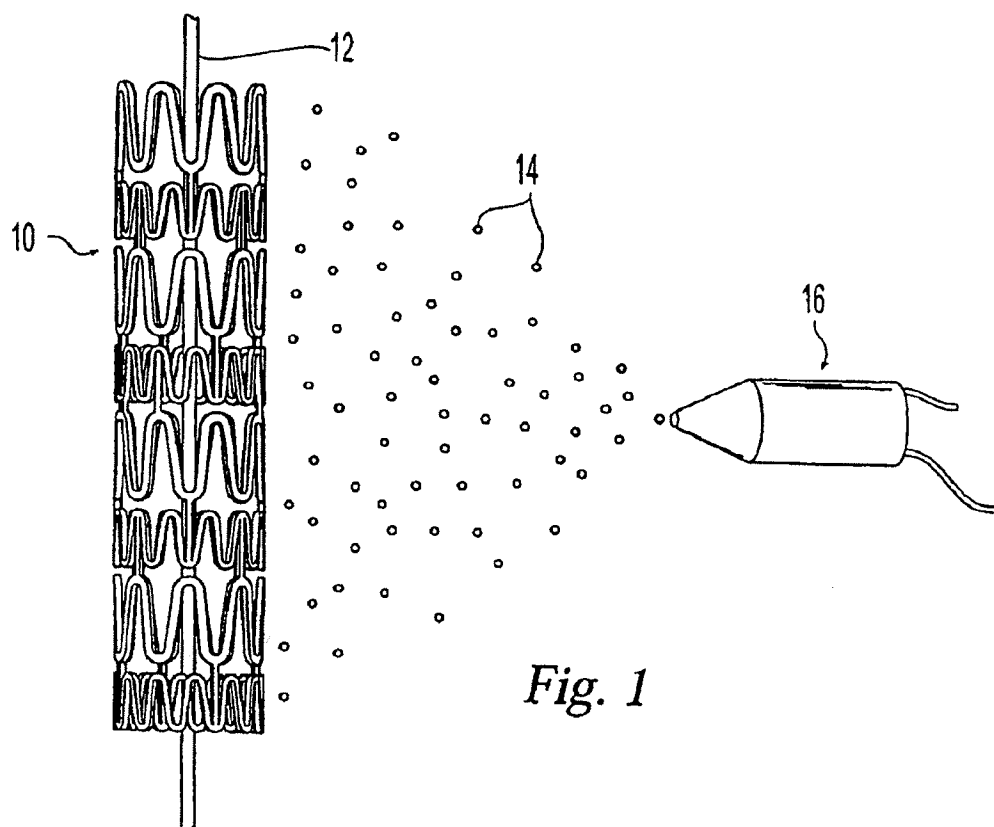


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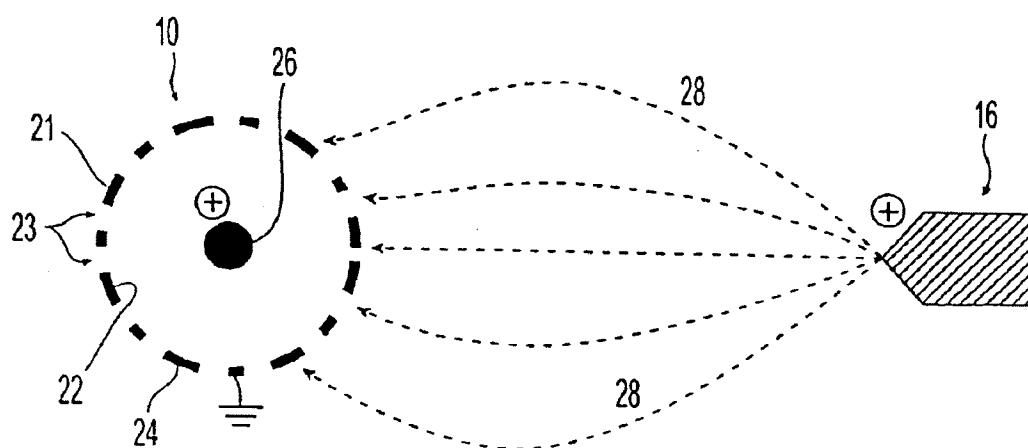
Mar. 1, 2005

Sheet 1 of 4

US 6,861,088 B2



*Fig. 1*



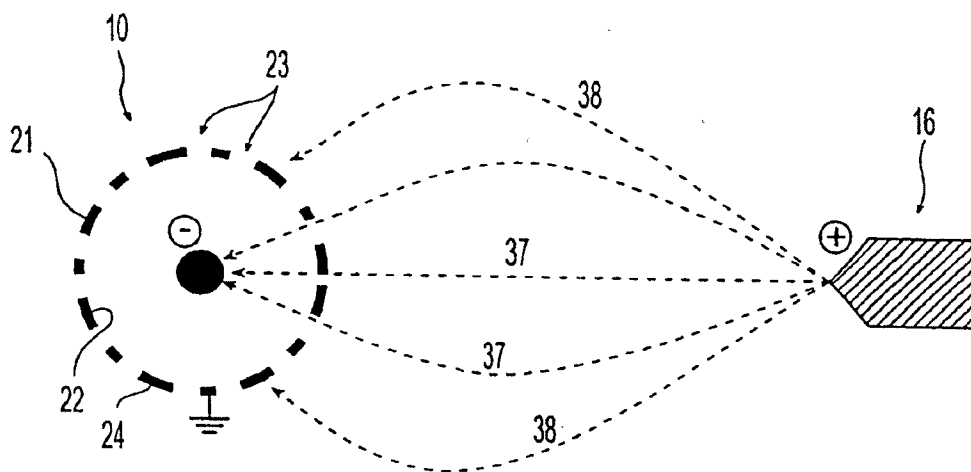
*Fig. 2*

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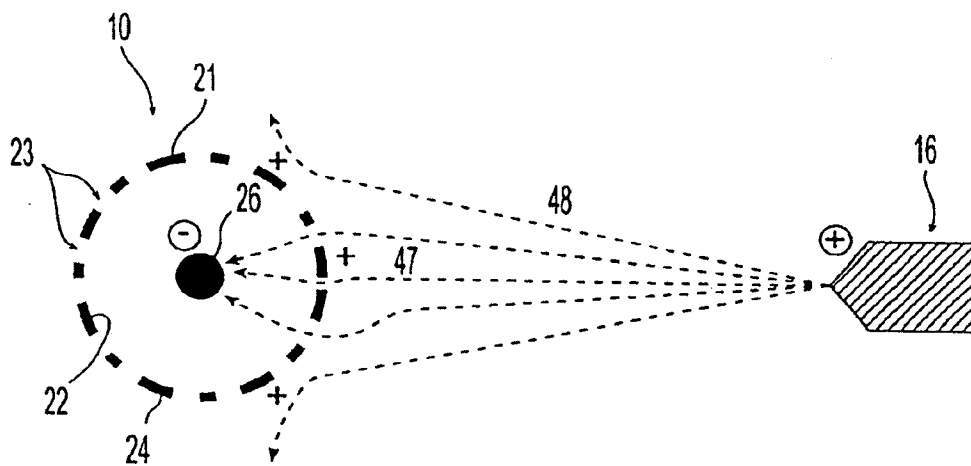
Mar. 1, 2005

Sheet 2 of 4

**US 6,861,088 B2**



*Fig. 3*



*Fig. 4*

U.S. Patent

Mar. 1, 2005

Sheet 3 of 4

US 6,861,088 B2

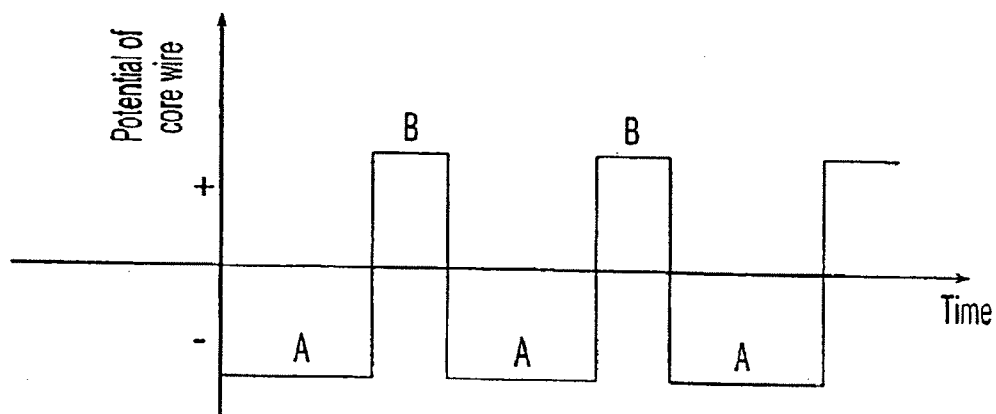


Fig. 5

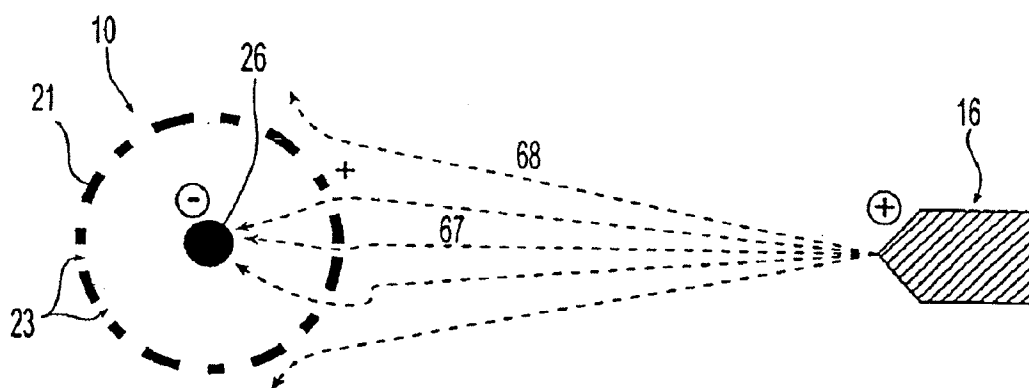


Fig. 6A

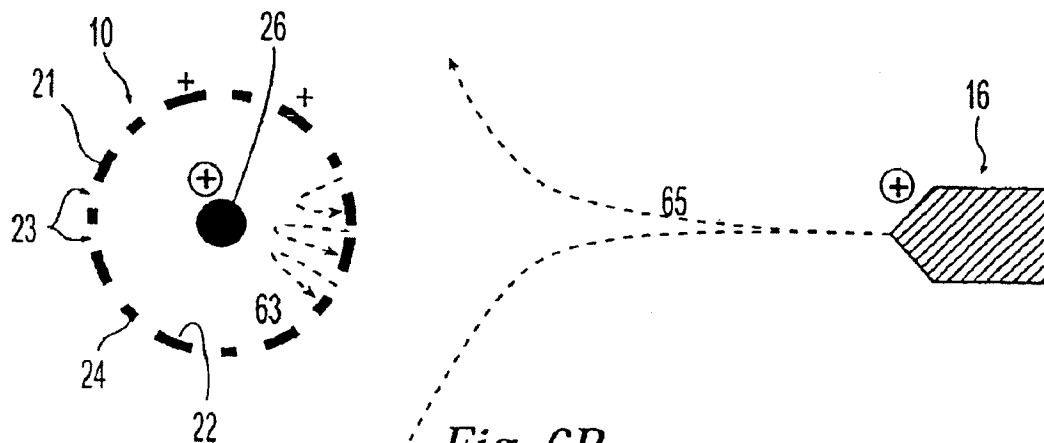


Fig. 6B

U.S. Patent

Mar. 1, 2005

Sheet 4 of 4

US 6,861,088 B2

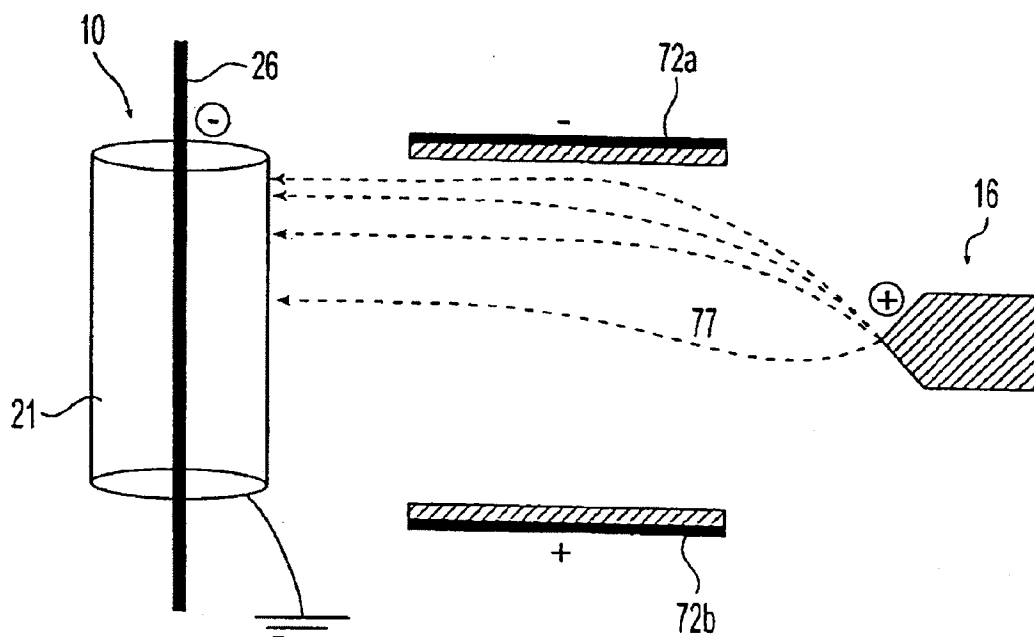


Fig. 7

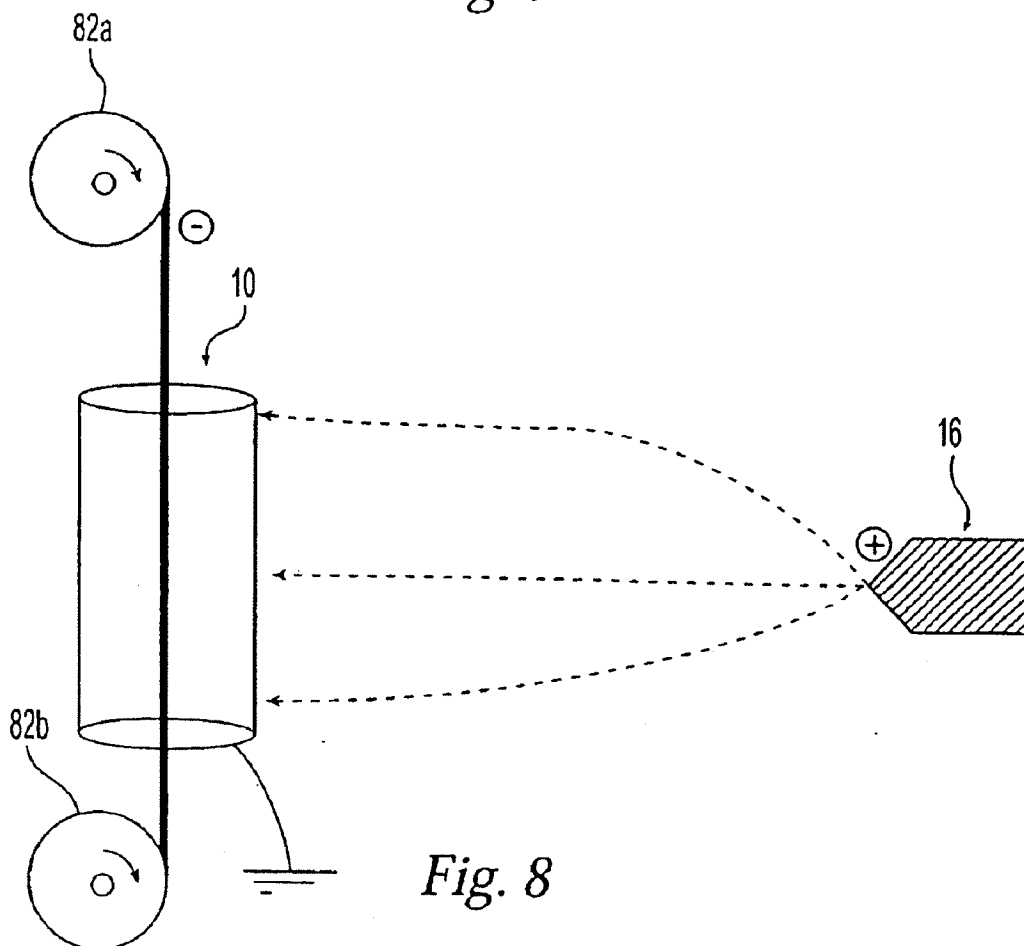


Fig. 8

US 6,861,088 B2

1

## METHOD FOR SPRAY-COATING A MEDICAL DEVICE HAVING A TUBULAR WALL SUCH AS A STENT

This application is a continuation application of U.S. application Ser. No. 10/109,073, filed Mar. 28, 2002, now U.S. Pat. No. 6,743,463 and is incorporated herein by reference in its entirety.

### FIELD OF THE INVENTION

The invention relates generally to a method for coating a stent or a medical device having a tubular wall. More particularly, the invention is directed to a method for electrostatic spray-coating a stent or a medical device having a tubular wall.

### BACKGROUND OF THE INVENTION

Medical devices, such as implantable stents, have been coated with a coating comprising a biocompatible polymer to reduce adverse physiological reactions, such as restenosis, caused by uncoated surfaces of medical devices inserted or implanted in patient's body. Also, the coating can incorporate a biologically active material. For example, implanted stents have been used to carry medicinal agents, such as thrombolytic agents. See, U.S. Pat. No. 6,099,562 to Ding et al., U.S. Pat. No. 5,879,697 to Ding et al., Pinchuk to U.S. Pat. No. 5,092,877, U.S. Pat. No. 5,304,121 to Sahatjian.

Such coatings have been applied to the surface of a medical device by various methods, e.g., spray coating and dip coating. When a tubular wall, such as a stent, having openings therein is coated by conventional methods, it has been extremely difficult to coat only the inner surface of a tubular wall without coating the outer surface and vice versa. Also, the ratio of coating thickness placed on the inner surface of the tubular wall and placed on the outer surface of the tubular wall created by a conventional method is fixed and cannot be varied. For example, when a spray coating method is employed to coat such a tubular wall, the ratio of coating thickness depends on the configuration of the tubular wall, specifically, the size and shape of the openings therein. Accordingly, this ratio cannot be controlled. When a dip coating method is employed, the thickness of the coating on the inner surface and the outer surface is the same and cannot be varied. Also, conventional coating methods lack the ability to coat a tubular wall so that the coating thickness along the longitudinal axis of the tubular wall is varied.

Furthermore, in some medical devices having a tubular wall, all of the surfaces of the medical device or portions thereof may not need to be coated, or may not need to be coated with a coating comprising a biologically active material. For instance, the inner surface of a stent does not have to be coated with a coating containing a biologically active material when the biologically active material is intended to be delivered to a body lumen wall, which only directly contacts the outer surface of the stent. The inner surface of the stent does not come in direct contact with the body lumen wall and does not apply the biologically active material to the body lumen wall. On the other hand, if the biologically active material is intended to be delivered to a body fluid rather than a body lumen wall, then the coating containing the biologically active material should be placed on the inner surface of the stent wall but is not needed on the outer surface.

Also, in some instances, a release profile of a biologically active material can be optimized by varying coating thickness along longitudinal axis of the tubular wall. Specifically,

2

in some stents, the amount of a coating containing a biologically active material may be preferably increased at the end sections of the tubular wall or stents as compared to the middle portion to reduce a risk of restenosis caused at the end sections.

In addition, coatings on different portions of the tubular wall may require different physical properties. For example, an expandable stent must be put in its unexpanded state or "crimped" before it is delivered to a body lumen. Thus, the coating on portions of the stent which contact each other in the stent's crimping state must not stick to each other and cause damage. In the case of a balloon expandable stent, the inner surface of the stent that contacts the balloon must not stick to the balloon during expansion. On the other hand, it is desirable to provide a relatively soft or "sticky" coating on the outer surface because it comes in direct contact with a body lumen wall.

Accordingly, there is a need for a method of coating a medical device comprising a tubular wall, such as a stent, that can control the thickness of coating on inner surface and outer surface. Furthermore, there is also a need for a method of coating a tubular wall, such as a stent, that can vary the thickness of coating along the longitudinal axis of the structure.

### SUMMARY OF THE INVENTION

This and other objectives are accomplished by the present invention. To achieve these objectives, we have developed a method which is efficient to realize a controlled thickness of a coating on at least a portion of a medical device comprising a tubular wall, such as a stent, having an inner surface, an outer surface and openings therein. Specifically, in the method of the present invention, the tubular wall is grounded or electrically charged and a conductive core wire is located axially through the tubular wall. A potential is applied to the conductive core wire to impart an electrical charge to the conductive core wire. The tubular wall is exposed to an electrically charged coating formulation, and the charged coating formulation is deposited onto a portion of the tubular wall to form a coating on the tubular wall. In one embodiment, the tubular wall is grounded, and the conductive core wire and the coating formulation has the same electrical charge. In another embodiment, the tubular wall is grounded, and the conductive core wire and the coating formulation has opposite electrical charges. In yet another embodiment, the tubular wall and the coating formulation has the same electrical charge and the conductive core wire has an electrical charge opposite that of the tubular wall and the coating formulation. Alternatively, the potential applied to the conductive core wire may be pulsed to cyclically impart a positive electrical charge to the conductive core wire followed by a negative electrical charge.

In an embodiment, a core wire comprising a resistor material is located axially through the tubular wall instead of the conductive core wire, and a current is directed in the core wire. Two resistor wires may be located axially through the tubular wall.

Furthermore, in the method of the present invention, the core wire can be kept free of the coating formulation by, for example, using two bobbins, wherein one is feeding the core wire through the tubular wall and the other is winding the core wire. Also, in the method of the present invention, a pair of deflector plates can be used to direct the charged coating formulation.

### BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 depicts a perspective view of a spraying nozzle, particles or droplets of charged coating formulation, a stent and a core wire used in the method of the present invention.

US 6,861,088 B2

3

FIGS. 2-4 are illustrative cross-sectional views of a stent and a core wire along with a spray nozzle and representative routes of charged coating formulation in embodiments of the method of the present invention.

FIG. 5 is a graph showing a cyclic change of the electrical potential applied to the core wire in an embodiment of the method of the present invention.

FIGS. 6A and 6B are illustrative cross-sectional views of a stent and a core wire along with a spray nozzle and representative routes of the charged coating formulation for two different states in the embodiment of the method of the present invention shown in FIG. 5.

FIG. 7 is an illustrative view of a spraying nozzle, a stent, a core wire, a pair of deflector plates, and representative routes of sprayed charged coating formulation, that are arranged for another embodiment of the method of the present invention.

FIG. 8 is an illustrative view of a spraying nozzle, a stent, a core wire, a pair of bobbins, and representative routes of sprayed charged coating formulation in yet another embodiment of the method of the present invention.

#### DESCRIPTION OF THE PREFERRED EMBODIMENTS

In the method of the present invention, the amount of a coating formulation that is applied to a surface of a stent or tubular wall of a medical device is adjusted by employing the principles of electro-assisted spraying and a core wire located through the stent or tubular wall. The term "tubular wall" refers to a wall having a certain thickness configured in a shape of a tube or tubular structure. Such tubular structure may have a cross-section other than circle, such as an oval or square. In conventional electro-assisted spraying techniques, an electrically charged coating formulation is sprayed or applied to the surface of the device to be coated. The device is usually grounded or negatively charged. Since the coating formulation is a poor conductor, part of the electrical charge of the coating formulation is unable to escape. Therefore, those portions of the device surface that are coated with the coating formulation will have a higher potential than uncoated regions, and new particles or droplets of charged coating formulation applied to the device will be deflected to those uncoated regions of the device surface. In such method, the amount of coating formulation applied to the surface of the device tends to be uniformly spread over the entire surface. In contrast as explained further below, by locating an electrically charged core wire through the stent or tubular wall of the device, the amount of coating formulation applied on different surfaces or parts of a surface of the device can be varied.

In one embodiment of the present invention, the coating formulation is in a form of droplets. In other embodiments of the present invention, the coating formulation is in a form of dry or wet powder-particles.

Referring to FIG. 1, which depicts a perspective view of an arrangement for the method of the present invention wherein a conductive core wire 12 is located axially through a stent 10. Preferably, the core wire is located through the geometric center of the stent. A spray nozzle 16 is placed in proximity of the stent 10 and an electrically charged coating formulation 14 is sprayed to the stent 10.

In an embodiment shown in FIG. 2, a stent 10 comprises a stent wall 21 having an inner surface 22, an outer surface 24 and openings therein 23. The stent wall 21 is grounded by a ground line so that it becomes electrically neutral. A potential is applied to a conductive core wire 26 located

4

axially through the geometric center of the stent 10 to impart a positive electrical charge to the conductive core wire 26. The coating formulation is positively charged and sprayed from the nozzle 16 toward the stent 10. Because of its positive electrical charge, the sprayed coating formulation is attracted to the grounded stent 10 and is deposited on the outer surface 24 and side portions of the openings 23 of the stent wall 21. Representative routes of the sprayed charged coating formulation are shown as the arrows 28. The positively charged coating formulation does not enter the openings 23 due to the electrical repulsion of the positively charged core wire. Therefore, the electrically charged coating formulation is deposited only on the outer surface 24 and the side portions of the openings 23 of the stent wall 21, and the inner surface 22 of the stent wall 21 is maintained substantially free of coating.

In an embodiment shown in FIG. 3, a stent 10 comprises a stent wall 21 having an inner surface 22, an outer surface 24 and openings therein 23. The stent wall 21 is grounded by a ground line so that it becomes electrically neutral. A conductive core wire 26 located axially through the geometric center of the stent 10 is negatively charged. The coating formulation is positively charged and sprayed from the nozzle 16 toward the stent 10. Because of its positive electrical charge, the sprayed coating formulation is attracted to the grounded stent wall 21. Some of the coating formulation is deposited on the outer surface 24 of the stent wall 21, and some of the coating formulation passes through the openings 23. Representative routes of the coating formulation are shown as the arrows 38. When the electrically charged coating formulation enters the openings 23, it is accelerated by virtue of the electrical forces of attraction and are attracted toward the conductive core wire 26. Therefore, the coating formulation is deposited only on the outer surface 24 of the stent wall 21, and the side portion of the openings 23 and the inner surface 22 of the stent are maintained substantially free of coating.

The embodiment shown in FIG. 4 is illustrative of how the method of the invention can be used to control how much coating is applied to the surface of a stent or a tubular wall. In this embodiment, a stent 10 comprises a stent wall 21 having an inner surface 22, an outer surface 24 and openings therein 23. The stent wall 21 is positively charged although its electrical potential is not high. A conductive core wire 26 located axially through the geometric center of the stent 10 is negatively charged. The coating formulation is positively charged and sprayed from the nozzle 16 toward the stent 10. Because of its positive electrical charge although the coating formulation is sprayed toward the stent 10, it is repelled by the positively charged stent 10. Representative routes of the coating formulation are shown as the arrows 48. When the coating formulation enters the opening 23, the coating formulation is attracted to the negatively charged conductive core wire 16 as shown by arrows 47. Therefore, the coating formulation is not deposited either on the inner surface 22 or on the outer surface 24 of the stent wall 21, and the stent is maintained substantially free of coating. This embodiment may be used to stop further coating formulation from being deposited, for example when a certain amount of coating has been reached. Also, this embodiment may be used to temporarily stop coating the device for a period without stopping a continuous stable output from the nozzle.

In an embodiment shown in FIGS. 6A and 6B, a stent 10 comprises a stent wall 21 having an inner surface 22, an outer surface 24 and openings therein 23. The stent wall 21 is positively charged although its electrical potential is not high. A conductive core wire 26 is located axially through

US 6,861,088 B2

5

the geometric center of the stent 10. The coating formulation is positively charged and sprayed from the nozzle 16 toward the stent 10. The electrical potential applied to the conductive core wire 26 is repeatedly alternated between positive and negative as shown in the graph of FIG. 5. In FIG. 5, at first, the electrical potential of the conductive core wire is negative (State A) for a certain period, and changes to positive (State B), and again changes to negative (State A). States A and B are repeated in turn. FIG. 6A shows State A, wherein the stent wall 21 is positively charged (the electrical potential is not high), and the conductive core wire 26 is negatively charged. The coating formulation is positively charged and sprayed from the nozzle 16 toward the stent 10. Because of its positive electrical charge, although the coating formulation is sprayed toward the stent 10, majority of particles or droplets are repelled by the positively charged stent 10 as shown arrows 68. When particles or droplets of the coating formulation enter in the openings 23, the particles or droplets are attracted to the negatively charged conductive core wire 16 as shown by arrows 67. Therefore, the coating formulation are not deposited either on the inner surface 22 or on the outer surface 24 of the stent wall 21, and the stent is maintained substantially free of coating.

FIG. 6B shows State B, wherein the stent wall 21 is still positively charged as in State A, but the conductive core wire 26 is also positively charged. The electrical potential of the conductive core wire 26 is higher than that of the stent wall 21. The coating formulation is positively charged and sprayed from the nozzle 16 toward the stent 10. Because of its positive electrical charge, although the coating formulation is sprayed toward the stent 10, it is repelled by the positively charged stent 10 as shown by arrows 65. However, there is the coating formulation inside the stent 10 which was being attracted to but had not yet reached the then-negatively charged conductive core wire 26 in State A. The coating formulation inside the stent 10 is repelled by the core wire 26, which is now positively charged, and the coating formulation is deposited on the inner surface 22 of the stent wall 21 in State B. Therefore, in this embodiment, the coating formulation is deposited on the inner surface 22, and the outer surface 24 of the stent wall 21 is maintained substantially free of coating. Skilled artisans can optimize the electrical potentials (voltage) of the conductive core wire 26, the stent 10 and the coating formulation and the cycle (frequency) of the potential change to adjust the amount of coating applied to the inner surface 22 of the stent wall 21. Generally, the time period of State A is longer than that of State B. The period of State A is preferably long enough for sufficient amount of coating formulation to enter in the stent wall 21 through the openings 23 but shorter than necessary for the coating formulation to reach the conductive core wire 26. The period of State B is preferably not more than enough for substantially all coating formulation inside the stent wall 21 to be deposited on the inner surface 22 of the stent wall 21.

Each embodiment of the method of the present invention explained above can be conducted alone. The embodiment shown in FIG. 2 can be used to coat the outer surface and the side portions of the openings of a stent wall. The embodiment shown in FIG. 3 can be used to coat the outer surface of a stent wall. The embodiment shown in FIGS. 6A and 6B can be used to coat the inner surface of a stent wall.

Also, however, those embodiments may be combined, if desired. Particularly, the electrical potential applied to the stent wall may be repeatedly alternated between neutral and positive, and so may the electrical potential applied to the conductive core wire. By adjusting the frequency of the

6

alternation and each electrical potential (voltage), it is possible to obtain any ratio of coating thickness on the inner surface, the outer surface and the side portions of the openings of the stent wall by using a continuous flow of sprayed coating formulation. For example, the following states may be employed to coat the device. Each state is part of a cycle, which can be repeated. During each of the states, the coating formulation remains positively charged:

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- State A: The stent wall has a positive electrical charge, but the potential applied to it is lower than that of the coating formulation. The conductive core wire has a negative electrical charge. (See FIG. 6A)
- State B: The stent wall has a positive electrical charge, and the conductive core wire has a positive electrical charge. The potential of the stent wall is lower than that of the coating formulation and the conductive core wire. (See FIG. 6B)
- State C: The stent wall is grounded, and the conductive core wire has a positive electrical charge. (See FIG. 2)
- State D: The stent wall is grounded, and the conductive core wire has a negative electrical charge. (See FIG. 3)
- State E: The stent wall has a positive electrical charge, but the potential applied to it is lower than that of the coating formulation. The conductive core wire has a negative electrical charge. (See FIG. 4)
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For example, arrangement of each electrical potential can be periodically switched starting from State A and changed to B, C, D, E and returning to A. During the period of States A-B, the coating formulation is deposited to the inner surface of the stent wall. During the period of State C, the coating formulation is deposited to the outer surface and side of the openings of the stent wall. Then, during the period of State D, the coating formulation is deposited to the outer surface of the stent wall, and during the period of State E, the coating formulation is not deposited to the stent wall. To increase the amount of coating placed on the inner surface, the length of time in States A+B should be increased. Likewise, to increase the amount of coating placed on the outer surface, the period of time in States C+D should be increased.

Moreover, the coating formulation may be negatively charged instead of being positively charged. If the coating formulation is negatively charged, then the stent is grounded or negatively charged, and the electrical potentials of the conductive core wire explained in the above embodiments are reversed.

Further, by adjusting time necessary for the coating formulation to reach to the surface to be coated in the above embodiments, it is possible to control the wetness of the coating formulation that arrive at a surface. The time can be adjusted by increasing or decreasing the field strength, specifically the electrical potentials of the coating formulation, the stent and the conductive core wire. If it takes longer for the coating formulation to get from the nozzle to the surface, then the coating formulation is dryer when it reaches the surface. If it takes less time for the coating formulation to get from nozzle to the surface, then the coating formulation is wetter when it reaches the surface. An appropriate wetness of the coating formulation must be chosen to obtain a coating layer which has desired physical properties and desired release profile of the biologically active material. For example, by choosing an appropriate wetness of the coating formulation in liquid form, it is possible to control the coating porosity. Such ability to control porosity is useful for preparing a coating for release of a biologically active material.

In embodiments of the method of the present invention a stent can be coated with a multiple coating layers of the



US 6,861,088 B2

7

same coating formulation. Such coating layers may be made by using the above mentioned method repeatedly. The thickness of each coating layer can be controlled as explained above. Also, the coating comprises various coating layers of different coating formulations. Such different coating layers can be efficiently made by using the present invention. For example, a first nozzle containing a first coating formulation may be first used to coat the outer surface of a stent by the above-mentioned embodiment of the method of the present invention, and then a second nozzle containing a second coating formulation may be used to coat the outer surface which is already coated with the first coating formulation. If desired, it is possible to coat a surface with the first coating formulation and coat the other surface with the second coating formulation which is different from the first coating formulation.

In addition to controlling the ratio of coating thickness on the inner surface, the outer surface and the side portions of the openings of the stent wall, the coating thickness along the longitudinal axis of a stent or a tubular wall can be controlled by an embodiment of the method of the present invention. Referring to FIG. 7, a pair of deflector plates 72a and 72b are added to an embodiment of the present invention shown in FIG. 3. The pair of deflector plates are a first deflector plate 72a having a negative electrical charge and a second deflector plate 72b having a positive electrical charge, which are parallel to each other. The pair of deflector plates 72a, 72b are placed parallel to the direction in which the coating formulation is sprayed from the nozzle 16 toward the stent 10. The positively charged coating formulation is attracted to the negatively charged deflector plate 72a and the course of the charged coating formulation is deflected toward the deflector plate 72a as shown by arrow 77. However, the electrical potential between the deflector plates 72a and 72b is so small that a majority of particles or droplets of the coating formulation do not contact the negatively charged deflector plate 72a. The distribution of the coating formulation on the stent wall 21 in its longitudinal direction can be controlled by using the deflector plates. For example, a stent having a coating which covers only one edge or end section of the stent can be obtained. If the potential is reversed, then the other edge or end section will also be covered by the coating, and a stent having a thicker coating at both end sections and thinner coating in the middle section can be obtained. The term "end section" of the outer surface refers to that part of the surface which extends from an end section or edge of a stent or a tubular wall up to about 25%, preferably from about 3% to about 20% of the entire length of the outer surface. The term "middle section" refers to the remainder of the outer surface that is surrounded by the end sections as defined above.

When the potential is reversed, the coating formulation may be switched from the first coating formulation to the second coating formulation so that a tubular wall can have a different type of coating on its end sections. By using different electrical potentials and varying the time such potentials are applied, sophisticated control of the coating can be achieved. For example, coating only a horizontal belt-like portion of the tubular wall or horizontal stripes of the tubular wall, is possible by adjusting the potential between the pair of deflector plates and adjusting the position of the deflector plates relative to the tubular wall.

When the electrical charge of the conductive core wire is opposite to that of the sprayed coating formulation, the coating formulation can be deposited on the conductive core wire in the method of the present invention. Since the coating formulation has poor conductivity, the electrical

8

potential of the wire becomes weaker as more coating formulation accumulates on the wire. To prevent such weakening potential of the conductive core wire, the wire is preferably kept substantially free from the coating formulation. For example, a pair of bobbins can be used to feed new conductive core wire through a stent as shown in FIG. 8. A first bobbin 82a on which a substantial length of conductive core wire is wound is one side of the stent 10 and the conductive core wire 26 is passed axially through the stent 10 and the other end section of the conductive core wire 26 is connected to a second bobbin 82b. As a portion of the conductive core wire is constantly unwound from the first bobbin 82a and fed through the stent 10, the conductive core wire covered with the coating formulation is removed and connected to the second bobbin 82b.

In one embodiment of the method of the present invention, a core wire made of a resistor material is used instead of a conductive core wire, and a current is directed through the wire. Since the potential of the core wire comprised of a resistor material is a function of the longitudinal position along the core wire, more electrically charged coating formulation is deposited on the portion of the surface of the tubular wall that is closer to the part of the core wire having higher opposite potential to the charged coating formulation. If two parallel core wires of resistor material are provided in a stent wherein opposing currents are directed, a stent having thicker coating at both end sections and thinner coating in the middle section can be obtained. A pair of bobbins or a pair of deflector plates explained above can also be used for core wires made of a resistor material.

Although the above embodiments of the method of the present invention are explained using a stent as an example of a medical device having a tubular wall, the method of the present invention can be used generally for coating at least a portion of a surface of a medical device comprising a tubular wall having an inner surface and an outer surface and openings therein. A preferable medical device is designed to be inserted or implanted into the body of a patient. Such medical devices suitable for the present invention include, but are not limited to, stents, vascular or other grafts, and filters, such as blood filters.

Medical devices which are particularly suitable for the present invention include stents, for example, vascular stents such as self-expanding stents and balloon expandable stents. Stents suitable for the present invention include any stent for medical purposes, which are known to the skilled artisans. Particularly the method of the present invention is useful for coating stents having intricate surfaces. Examples of self-expanding stents useful in the present invention are illustrated in U.S. Pat. Nos. 4,655,771 and 4,954,126 issued to Wallsten and U.S. Pat. No. 5,061,275 issued to Wallsten et al. Examples of appropriate balloon-expandable stents are shown in U.S. Pat. No. 5,449,373 issued to Pinchasik et al.

The medical devices suitable for the present invention may be fabricated from conductive materials, such as conductive ceramic, polymeric and metallic materials. The surface(s) of the medical devices to be coated using the process of the present invention should be fabricated from conductive materials. Suitable metallic materials include metals and alloys based on titanium (such as nitinol, nickel titanium alloys, thermo-memory alloy materials), stainless steel, tantalum, nickel-chrome, or certain cobalt alloys including cobalt-chromium-nickel alloys such as Elgiloy® and Phynox®. Metallic materials also include clad composite filaments, such as those disclosed in WO 94/16646. An example of a suitable ceramic is carbide. Polymers can be

US 6,861,088 B2

9

used to fabricate the medical device when they are conductive. These include polymers filled with carbon-nanotubes. Carbon-nanotubes are commercially available, e.g., from CARBOLEX. Only the surface to be coated rather than entire medical device may be fabricated from a conductive material.

The core wire can be made of a conductive material. The surface of core wire should be conductive. Suitable conductive materials include those described materials for the medical device. In an embodiment of the method of the present invention, the core wire is made of a resistor material, such as carbon, a polymer filled with carbon nanotubes.

Any spraying nozzle or spraying device that can spray coating formulation and create particles or droplets of an appropriate size and of appropriate electrical charge is useful for the method of the present invention. Examples of such spraying nozzle are disclosed in U.S. Pat. No. 4,341,347 to DeVittorio, U.S. Pat. No. 4,004,733 to Law, U.S. Pat. No. 4,215,818 to Hopkinson, and U.S. Pat. No. 4,002,777 to Juvinal et al. One preferable example of a spraying nozzle that can be used in the method of the invention is an apparatus for electrophoretic spray-coating that is disclosed in U.S. Pat. No. 4,749,125, to Escallon et al.

Coating formulations that are useful for the method of the present invention may be a solution or a suspension comprising a polymeric material and solvent or may be powder comprising a polymeric material. The polymeric material useful for forming the coating formulation should be ones that are biocompatible and avoids irritation to body tissue. Preferably the polymeric materials are biostable ones such as polyurethanes, silicones (e.g., polysiloxanes and substituted polysiloxanes), and polyesters. Also preferable as a polymeric material is styrene-isobutylene copolymers. Other polymers which can be used include ones that can be dissolved and cured or polymerized on the medical device or polymers having relatively low melting points that can be blended with biologically active materials. Additional suitable polymers include, thermoplastic elastomers in general, polyolefins, polyisobutylene, ethylene-alphaolefin copolymers, acrylic polymers and copolymers, vinyl halide polymers and copolymers such as polyvinyl chloride, polyvinyl ethers such as polyvinyl methyl ether, polyvinylidene halides such as polyvinylidene fluoride and polyvinylidene chloride, polyacrylonitrile, polyvinyl ketones, polyvinyl aromatics such as polystyrene, polyvinyl esters such as polyvinyl acetate, copolymers of vinyl monomers, copolymers of vinyl monomers and olefins such as ethylene-methyl methacrylate copolymers, acrylonitrile-styrene copolymers, ABS (acrylonitrile-butadiene-styrene) resins, ethylene-vinyl acetate copolymers, polyamides such as Nylon 66, Nylon 12 and polycaprolactone, alkyd resins, polycarbonates, polyoxymethylenes, polyimides, polyethers, epoxy resins, rayon-triacetate, cellulose, cellulose acetate, cellulose butyrate, cellulose acetate butyrate, cellophane, cellulose nitrate, cellulose propionate, cellulose ethers, carboxymethyl cellulose, collagens, chitins, polylactic acid, polyglycolic acid, polylactic acid-polyethylene oxide copolymers, EPDM (ethylene-propylene-diene) rubbers, fluorosilicones, polyethylene glycol, polysaccharides, phospholipids, combinations of the foregoing.

More preferably for medical devices which undergo mechanical challenges, e.g. expansion and contraction, the polymeric materials should be selected from elastomeric polymers such as silicones (e.g. polysiloxanes and substituted polysiloxanes), polyurethanes, thermoplastic elastomers, ethylene vinyl acetate copolymers, polyolefin

10

elastomers, and EPDM rubbers. Because of the elastic nature of these polymers, the coating adheres better to the surface of the medical device when the device is subjected to forces, stress or mechanical challenge.

Furthermore, although the invention can be practiced by using a single type of polymer to form the coating layer(s), various combinations of polymers can be employed. The appropriate mixture of polymers can be coordinated with biologically active materials of interest to produce desired effects when coated on a medical device in accordance with the invention.

Coating formulations useful for the present invention may contain a nanocomposite instead of or in addition to a polymeric material explained above. "Nanocomposite" is a term of art that refers to a composition comprising a polymeric material and relatively small amounts (generally less than about 10% by weight) of nanometer-sized (average size smaller than 1 micrometer) mineral clay or nanosized ceramic particles dispersed therein. Sometimes nanocomposites are referred to as "nanoclay" or "nanoceramic". For example, nanocomposites are disclosed in WO 931014118, U.S. Pat. Nos. 5,385,776, and 6,251,980.

Solvents suitable for forming the coating formulation are ones which can dissolve the polymeric material into solution or form dispersions of the polymeric material in the solvent. Any solvent which does not alter or adversely impact the therapeutic properties of the biologically active material can be employed in the method of the present invention. Examples of useful solvents include tetrahydrofuran, chloroform, toluene, acetone, isooctane, 1,1,1-trichloroethane, and mixture thereof. Preferably, chloroform or tetrahydrofuran is used as the solvent in the method of the present invention.

Coating formulations useful for the present invention that are in powder form can comprise a polymeric material as explained above. The powder is preferably comprised of particles having an average diameter from about 0.5  $\mu\text{m}$  to about 250  $\mu\text{m}$ . Generally, the resulting surface of the coating is smoother when the powder of the coating formulation used for the coating has a smaller average particle size. After the spray-coating step using the powder coating formulation, the tubular wall coated with the powder coating formulation is heat-treated, for example using IR heating.

Even when the coating formulation used for the present invention contains a solvent, it is possible to control the process to dry the sprayed coating formulation before they reach the tubular wall of the medical device by controlling the method as explained earlier. In this manner, results similar to those of the process using dry-powder coating formulation can be obtained by using the coating formulation containing a solvent.

Coating formulations useful for the method of the present invention may also comprise a biologically active material. The term "biologically active material" encompasses therapeutic agents, such as drugs, and also genetic materials and biological materials. The genetic materials mean DNA or RNA, including, without limitation, of DNA/RNA encoding a useful protein stated below, anti-sense DNA/RNA, intended to be inserted into a human body including viral vectors and non-viral vectors. Examples of DNA suitable for the present invention include DNA encoding

anti-sense RNA

tRNA or rRNA to replace defective or deficient endogenous molecules

angiogenic factors including growth factors, such as acidic and basic fibroblast growth factors, vascular endothelial growth factor, epidermal growth factor, transforming

US 6,861,088 B2

11

growth factor  $\alpha$  and  $\beta$ , platelet-derived endothelial growth factor, platelet-derived growth factor, tumor necrosis factor  $\alpha$ , hepatocyte growth factor and insulin like growth factor cell ccle inhibitors including CD inhibitors

thymidine kinase ("TK") and other agents useful for interfering with cell proliferation, and

the family of bone morphogenic proteins ("BMP's") as explained below. Viral vectors include adenoviruses, gutted adenoviruses, adeno-associated virus, retroviruses, alpha virus (Semliki Forest, Sindbis, etc.), lentiviruses, herpes simplex virus, ex vivo modified cells (e.g., stem cells, fibroblasts, myoblasts, satellite cells, pericytes, cardiomyocytes, skeletal myocytes, macrophage), replication competent viruses (e.g., ONYX-015), and hybrid vectors. Non-viral vectors include artificial chromosomes and mini-chromosomes, plasmid DNA vectors (e.g., pCOR), cationic polymers (e.g., polyethyleneimine, polyethyleneimine (PEI)) graft copolymers (e.g., polyether-PEI and polyethylene oxide-PEI), neutral polymers PVP, SP1017 (SUPRATEK), lipids or lipoplexes, nanoparticles and microparticles with and without targeting sequences such as the protein transduction domain (PTD).

The biological materials include cells, yeasts, bacteria, proteins, peptides, cytokines and hormones. Examples for peptides and proteins include growth factors (FGF, FGF-1, FGF-2, VEGF, Endothelial Mitogenic Growth Factors, and epidermal growth factors, transforming growth factor  $\alpha$  and  $\beta$ , platelet derived endothelial growth factor, platelet derived growth factor, tumor necrosis factor  $\alpha$ , hepatocyte growth factor and insulin like growth factor), transcription factors, protein kinases, CD inhibitors, thymidine kinase, and bone morphogenic proteins (BMP's), such as BMP-2, BMP-3, BMP-4, BMP-5, BMP-6 (Vgr-1), BMP-7 (OP-1), BMP-8, BMP-9, BMP-10, BMP-11, BMP-12, BMP-13, BMP-14, BMP-15, and BMP-16. Currently preferred BMP's are BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7. Alternatively or in addition, molecules capable of inducing an upstream or downstream effect of a BMP can be provided. Such molecules include any of the "hedgehog" proteins, or the DNA's encoding them. These dimeric proteins can be provided as homodimers, heterodimers, or combinations thereof, alone or together with other molecules. Cells can be of human origin (autologous or allogeneic) or from an animal source (xenogeneic), genetically engineered, if desired, to deliver proteins of interest at the transplant site. The delivery media can be formulated as needed to maintain cell function and viability. Cells include whole bone marrow, bone marrow derived mono-nuclear cells, progenitor cells (e.g., endothelial progenitor cells) stem cells (e.g., mesenchymal, hematopoietic, neuronal), pluripotent stem cells, fibroblasts, macrophage, and satellite cells.

Biologically active material also includes non-genetic therapeutic agents, such as:

anti-thrombogenic agents such as heparin, heparin derivatives, urokinase, and PPACK (dextrophenylalanine proline arginine chloromethylketone);

anti-proliferative agents such as enoxaprin, angiopeptin, or monoclonal antibodies capable of blocking smooth muscle cell proliferation, hirudin, and acetylsalicylic acid, amlodipine and doxazosin;

anti-inflammatory agents such as glucocorticoids, betamethasone, dexamethasone, prednisolone, corticosterone, budesonide, estrogen, sulfasalazine, and mesalamine;

immunosuppressants such as sirolimus (RAPAMYCIN), tacrolimus, everolimus and dexamethasone,

12

antineoplastic/antiproliferative/anti-mitotic agents such as paclitaxel, 5-fluorouracil, cisplatin, vinblastine, vincristine, epothilones, methotrexate, azathioprine, halofuginone, adriamycin, actinomycin and mutamycin; endostatin, angiostatin and thymidine kinase inhibitors, and its analogs or derivatives;

anesthetic agents such as lidocaine, bupivacaine, and ropivacaine;

anti-coagulants such as D-Phe-Pro-Arg chloromethyl keton, an RGD peptide-containing compound, heparin, anti-thrombin compounds, platelet receptor antagonists, anti-thrombin antidotes, anti-platelet receptor antibodies, aspirin (aspirin is also classified as an analgesic, anti-pyretic and anti-inflammatory drug), dipyridamole, protamine, hirudin, prostaglandin inhibitors, platelet inhibitors and tick antiplatelet peptides;

vascular cell growth promoters such as growth factors, Vascular Endothelial Growth Factors (VEGF, all types including VEGF-2), growth factor receptors, transcriptional activators, and translational promoters;

vascular cell growth inhibitors such as antiproliferative agents, growth factor inhibitors, growth factor receptor antagonists, transcriptional repressors, translational repressors, replication inhibitors, inhibitory antibodies, antibodies directed against growth factors, bifunctional molecules consisting of a growth factor and a cytotoxin, bifunctional molecules consisting of an antibody and a cytotoxin;

cholesterol-lowering agents; vasodilating agents; and agents which interfere with endogenous vasoactive mechanisms; anti-oxidants, such as probucol;

antibiotic agents, such as penicillin, cefoxitin, oxacillin, tobramycin

angiogenic substances, such as acidic and basic fibroblast growth factors, estrogen including estradiol (E2), estriol (E3) and 17-Beta Estradiol; and

drugs for heart failure, such as digoxin, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors including captopril and enalapril.

Also, the biologically active materials of the present invention include nitric oxide adducts, which prevent and/or treat adverse effects associated with use of a medical device in a patient, such as restenosis and damaged blood vessel surface. Typical nitric oxide adducts include nitroglycerin, sodium nitroprusside, S-nitroso-proteins, S-nitroso-thiols, long carbon-chain lipophilic S-nitrosothiols, S-nitrosodithiols, iron-nitrosyl compounds, thionitrates, thionitrates, sydnominines, furoxans, organic nitrates, and nitrosated amino acids, preferably mono- or polynitrosylated proteins, particularly polynitrosated albumin or polymers or aggregates thereof. The albumin is preferably human or bovine, including humanized bovine serum albumin. Such nitric oxide adducts are disclosed in U.S. Pat. No. 6,087,479 to Stamler et al. which is incorporated herein by reference.

A biologically active material may be encapsulated in micro or nano-capsules by the known methods.

The biologically active material can be used with (a) biologically non-active material(s) including a carrier or an excipient, such as sucrose acetate isobutyrate (SABER™ commercially available from SBS) ethanol, n-methyl pymolidone, dimethyl sulfoxide, benzyl benzoate, benzyl acetate, albumine, carbohydrate, and polysaccharide. Also, nanoparticles of the biologically active materials and non-active materials are useful for the coating formulation of the present invention.

US 6,861,088 B2

13

The description contained herein is for purposes of illustration and not for purposes of limitation. Changes and modifications may be made to the embodiments of the description and still be within the scope of the invention. Furthermore, obvious changes modifications or variations will occur to those skilled in the art. Also, all references cited above are incorporated herein in their entirety, for all purposes related to this disclosure.

We claim:

1. A method for coating a medical device comprising a tubular wall having an inner surface, an outer surface and openings therein, wherein the method comprises:

- (a) grounding or electrically charging the tubular wall;
- (b) providing a conductive core wire located axially through the tubular wall;
- (c) applying a potential to the conductive core wire to impart an electrical charge to the conductive core wire;
- (d) exposing the tubular wall to an electrically charged coating formulation comprising a biologically active material; and
- (e) depositing the coating formulation onto a portion of the tubular wall to form a coating on the tubular wall.

2. The method of claim 1, wherein the biologically active material comprises an immunosuppressant, an antiproliferative agent, or a combination thereof.

3. The method of claim 2, wherein the immunosuppressant comprises sirolimus, everolimus, tacrolimus, or a combination thereof.

4. The method of claim 2, wherein the antiproliferative agent comprises paclitaxel, an analog thereof, a derivative thereof, or a combination thereof.

5. The method of claim 1, wherein the biologically active material comprises genetic material.

6. The method of claim 1, wherein the coating formulation further comprises a polymeric material and a solvent.

7. The method of claim 1, wherein the tubular wall is grounded, and the conductive core wire and the coating formulation have the same electrical charge.

8. The method of claim 7, wherein the electrical charge of the coating formulation and the electrical charge of the conductive core wire are adjusted so that the charged coating formulation is deposited on the outer surface of the tubular wall and the inner surface remains substantially free of the charged coating formulation.

9. The method of claim 1, wherein the tubular wall is grounded, and the conductive core wire has an electrical charge opposite that of the coating formulation.

10. The method of claim 1, wherein the tubular wall comprises a geometric center, and the conductive core wire is located axially through the center of the tubular wall.

11. The method of claim 1, wherein the potential applied to the conductive core wire is pulsed to cyclically impart a positive electrical charge to the conductive core wire followed by a negative electrical charge.

12. The method of claim 11, wherein a positive electrical charge imparted to the conductive core wire is for a shorter duration than the negative electrical charge imparted to the conductive core wire.

13. The method of claim 11, wherein the coating formulation has a positive electrical charge, and an electrical potential applied to the tubular wall is repeatedly alternated between grounded and positively charged to deposit a desired amount of the coating formulation on each portion of the tubular wall.

14. The method of claim 1, wherein the conductive core wire is kept substantially free of the charged coating formulation.

14

15. The method of claim 1, wherein the conductive core wire has two ends and one end of the conductive core wire is connected to a first bobbin and the other end is connected to a second bobbin, wherein the conductive core wire is fed from the first bobbin through the tubular wall, and wherein the conductive core wire covered with the coating formulation is removed from the tubular wall by being connected to the second bobbin.

16. The method of claim 1, which further comprises directing the charged coating formulation by providing (a) a first deflector plate having a positive electrical charge and a second deflector plate having a negative electrical charge, which are placed parallel to each other and (b) applying the charged coating formulation between the plates.

17. A method for coating a medical device comprising a tubular wall having an inner surface, an outer surface and openings therein, wherein the method comprises:

- (a) grounding or electrically charging the tubular wall;
- (b) providing a first core wire comprising a resistor material located axially through the tubular wall;
- (c) directing a current through the first core wire;
- (d) creating an electrically charged coating formulation comprising a biologically active material; and
- (e) depositing the coating formulation onto the tubular wall to form a coating on the tubular wall.

18. The method of claim 17, wherein the coating formulation further comprises a polymeric material and a solvent.

19. The method of claim 17, wherein the tubular wall comprises two end sections and wherein a greater amount of coating formulation is applied to one end section than the other.

20. The method of claim 17, which further comprises providing a second core wire comprising a resistor material through the tubular wall wherein the second core wire is parallel to the first core wire; and directing a second current through the second core wire in direction opposite the first current.

21. The method of claim 17, wherein the first core wire is kept substantially free of the coating formulation.

22. The method of claim 17, wherein the first core wire comprising two ends and one end of the first core wire is connected to a first bobbin and the other end is connected to a second bobbin, wherein the first core wire is fed from the first bobbin through the tubular wall, and wherein the first core wire covered with the coating formulation is removed from the tubular wall by being connected to the second bobbin.

23. The method of claim 17, wherein the biologically active material comprises an immunosuppressant, an antiproliferative agent, or a combination thereof.

24. The method of claim 23, wherein the immunosuppressant comprises sirolimus, everolimus, tacrolimus, or a combination thereof.

25. The method of claim 23, wherein the antiproliferative agent comprises paclitaxel, an analog thereof, a derivative thereof, or a combination thereof.

26. The method of claim 23, wherein the coating formulation further comprises a polymeric material and a solvent.

27. The method of claim 17, wherein the biologically active material comprises genetic material.

28. A method for coating at least a portion of a stent, wherein the stent comprises a stent wall having an inner surface, an outer surface and openings therein, wherein the method comprises:

- (a) grounding or electrically charging the stent wall;
- (b) providing a conductive core wire located axially through the stent;

US 6,861,088 B2

15

- (c) applying a potential to the conductive core wire to impart an electrical charge to the conductive core wire;
- (d) exposing the stent to an electrically charged coating formulation comprising a biologically active material; and

- (e) depositing the charged coating formulation onto the stent portion to form a coating on the portion.

29. The method of claim 28, wherein the biologically active material comprises an immunosuppressant, an antiproliferative agent, or a combination thereof.

16

30. The method of claim 29, wherein the immunosuppressant comprises sirolimus, everolimus, tacrolimus, or a combination thereof.

31. The method of claim 29, wherein the antiproliferative agent comprises paclitaxel, an analog thereof, a derivative thereof, or a combination thereof.

32. The method of claim 28, wherein the biologically active material comprises genetic material.

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(12) **United States Patent**  
**Hossainy et al.**

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(45) **Date of Patent:** **\*Jun. 20, 2006**

(54) **STENT COATING**

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(57) **ABSTRACT**

A stent comprising a coating layer is disclosed. The coating layer has a hydrophobic component and a hydrophilic component, wherein a region of the coating layer on or about the outermost surface of the coating layer has a higher content or concentration of the hydrophilic component than the hydrophobic component.

**14 Claims, No Drawings**

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US 7,063,884 B2

1

## STENT COATING

## CROSS REFERENCE

This application is a continuation-in-part of application Ser. No. 10/375,620, filed on Feb. 26, 2003 now U.S. Pat. No. 6,926,919.

## BACKGROUND OF THE INVENTION

## 1. Field of the Invention

This invention is directed to coatings for drug delivery devices, such as drug eluting vascular stents, and methods for producing the same.

## 2. Description of the State of the Art

Percutaneous transluminal coronary angioplasty (PTCA) is a procedure for treating heart disease. A catheter assembly having a balloon portion is introduced percutaneously into the cardiovascular system of a patient via the brachial or femoral artery. The catheter assembly is advanced through the coronary vasculature until the balloon portion is positioned across the occlusive lesion. Once in position across the lesion, the balloon is inflated to a predetermined size to radially compress against the atherosclerotic plaque of the lesion to remodel the lumen wall. The balloon is then deflated to a smaller profile to allow the catheter to be withdrawn from the patient's vasculature.

A problem associated with the above procedure includes formation of intimal flaps or torn arterial linings which can collapse and occlude the conduit after the balloon is deflated. Moreover, thrombosis and restenosis of the artery may develop over several months after the procedure, which may require another angioplasty procedure or a surgical by-pass operation. To reduce the partial or total occlusion of the artery by the collapse of arterial lining and to reduce the chance of the development of thrombosis and restenosis, a stent is implanted in the lumen to maintain the vascular patency.

Stents are used not only as a mechanical intervention but also as a vehicle for providing biological therapy. As a mechanical intervention, stents act as scaffoldings, functioning to physically hold open and, if desired, to expand the wall of the passageway. Typically, stents are capable of being compressed, so that they can be inserted through small vessels via catheters, and then expanded to a larger diameter once they are at the desired location. Examples in patent literature disclosing stents which have been applied in PTCA procedures include stents illustrated in U.S. Pat. No. 4,733,665 issued to Palmaz, U.S. Pat. No. 4,800,882 issued to Gianturco, and U.S. Pat. No. 4,886,062 issued to Wiktor.

Biological therapy can be achieved by medicating the stents. Medicated stents provide for the local administration of a therapeutic substance at the diseased site. In order to provide an efficacious concentration to the treated site, systemic administration of such medication often produces adverse or toxic side effects for the patient. Local delivery is a preferred method of treatment in that smaller total levels of medication are administered in comparison to systemic dosages, but are concentrated at a specific site. Local delivery thus produces fewer side effects and achieves more favorable results. One proposed method for medicating stents involves the use of a polymeric carrier coated onto the surface of a stent. A solution which includes a solvent, a polymer dissolved in the solvent, and a therapeutic substance dispersed in the blend is applied to the stent. The

2

solvent is allowed to evaporate, leaving on the stent surface a coating of the polymer and the therapeutic substance impregnated in the polymer.

Local administration of therapeutic agents via stents has shown some favorable results in reducing restenosis. However, the properties of stent coatings can be improved. For example, when the outermost layer of the coating comprises a blend of hydrophobic and hydrophilic polymers, the hydrophobic polymers tend to bloom to coating-air interface. Yet, in many applications it is highly desirable to have hydrophilic polymers evolve at the coating-air interface to provide the stent coating with better blood compatibility, biological activity and non-fouling properties. Accordingly, the present invention discloses such improved stent coatings and methods for fabricating thereof.

## SUMMARY

A stent comprising a coating layer is disclosed, the coating layer having a hydrophobic component and a hydrophilic component, wherein a region of the coating layer on or about the outermost surface of the coating layer has a higher content or concentration of the hydrophilic component than the hydrophobic component and wherein the hydrophilic component has a solubility parameter higher than about  $8.5 \text{ (cal/cm}^3)^{1/2}$ . The hydrophobic and hydrophilic components can be in blended format in the coating layer. The hydrophobic and hydrophilic components can be bonded in the coating layer. The hydrophobic and hydrophilic components can be an interpenetrating polymer network. In some embodiments, the hydrophobic component has a solubility parameter less than about  $11.5 \text{ (cal/cm}^3)^{1/2}$ . The coating layer can include one or a combination of a primer layer, a reservoir layer including a drug and a topcoat layer.

## DETAILED DESCRIPTION

A coating or coating layer for an implantable medical device, such as a stent, according to one embodiment of the present invention, can include a drug-polymer layer (also referred to as "reservoir" or "reservoir layer") or alternatively a polymer free drug layer, an optional primer layer and an optional topcoat layer. The drug-polymer layer serves as a reservoir for the drug. The reservoir layer or the polymer free drug layer can be applied directly onto the stent surface. The optional topcoat layer, which can be essentially free from any drugs, serves as a rate limiting membrane which helps to control the rate of release of the drug. The optional primer layer can be applied on the stent surface to improve the adhesion of the drug-polymer layer or the polymer free drug layer to the stent.

The reservoir layer and the optional primer and topcoat layers of the coating can be formed on the stent by dissolving a polymer or a blend of polymers in a solvent, or a mixture of solvents, and applying the resulting polymer solution on the stent by spraying or immersing the stent in the solution. To incorporate a drug into the reservoir layer, the drug in a form of a solution can be combined with the polymer solution. Alternatively, to fabricate a polymer free drug layer, the drug can be dissolved in a suitable solvent or mixture of solvents, and the resulting drug solution can be applied on the stent by spraying or immersing the stent in the drug solution.

Instead of introducing the drug in a solution, the drug can be introduced as a colloid system, such as a suspension in an appropriate solvent phase. To make the suspension, the drug

US 7,063,884 B2

3

can be dispersed in the solvent phase using conventional techniques used in colloid chemistry. Depending on a variety of factors, e.g., the nature of the drug, those having ordinary skill in the art will select the suitable solvent to form the solvent phase of the suspension, as well as the quantity of the drug to be dispersed in the solvent phase. The suspension can be mixed with a polymer solution and the mixture can be applied on the stent as described above. Alternatively, the drug suspension can be applied on the stent without being mixed with the polymer solution.

The outermost layer of the stent coating can be either the topcoat layer or the reservoir layer (if the optional topcoat layer is not used). In some embodiments, the outermost layer of the stent coating is comprised of a blend of polymers, the blend to include one or more hydrophilic polymers and one or more hydrophobic polymers. In some embodiments, the mass ratio between the hydrophilic and hydrophobic polymers in the coating or the outermost layer of the coating can be typically between about 1:100 and 1:9.

Generally, hydrophobicity of a polymer or component in the coating can be gauged using the Hildebrand solubility parameter  $\delta$ . The term "Hildebrand solubility parameter" refers to a parameter measuring the cohesion of a substance. The  $\delta$  parameter is determined as follows:

$$\delta = (\Delta E/V)^{1/2}$$

where  $\delta$  is the solubility parameter,  $(\text{cal}/\text{cm}^3)^{1/2}$ ;  $\Delta E$  is the energy of vaporization,  $\text{cal}/\text{mole}$ ; and  $V$  is the molar volume,  $\text{cm}^3/\text{mole}$ .

Whichever polymer or component in the combination, mixture, blend, bonding or conjugation has the lower  $\delta$  value as compared to the  $\delta$  value of the other component is designated as hydrophobic, and the component with the higher  $\delta$  value is designated as hydrophilic. If more than two components or polymers are used such as in the combined, mixed, blended, bonded or conjugated chemical, then each can be ranked in order of its  $\delta$  value. For the practice of the present invention, the value of  $\delta$  of a particular component or polymer is inconsequential for classifying it as hydrophobic or hydrophilic so long as the difference in the  $\delta$  values of the two components or polymers is sufficient to allow the hydrophilic part or unit to migrate or bloom to the surface as described below. In some embodiment, the  $\delta$  value defining the boundary between hydrophobicity and hydrophilicity can be about  $8.0 (\text{cal}/\text{cm}^3)^{1/2}$  (i.e., the hydrophilic component is above about  $8.0 (\text{cal}/\text{cm}^3)^{1/2}$ . In some embodiments, the hydrophilic component can have a value above about 8.5, 9.0, 9.5, 10.0, 10.5, 11.0 or  $11.5 (\text{cal}/\text{cm}^3)^{1/2}$ . In some embodiments, the hydrophobic component can be below about 8.5, 9.0, 9.5, 10.0, 10.5, 11.0 or  $11.5 (\text{cal}/\text{cm}^3)^{1/2}$ . In some embodiments the hydrophilic component can be a non-fouling component, bioactive component and/or a biobeneficial component in addition to or in lieu of having the Hildebrand value(s) described above. In one embodiment, non-fouling is defined as not capable of adsorbing or attracting proteins, or adsorbing or attracting only a minimal amount of proteins, or less proteins than a compound not having a non-fouling moiety. A "bioactive component" can be a component or moiety that can be combined with a polymer and provides a therapeutic effect, a prophylactic effect, both a therapeutic and a prophylactic effect, or other biologically active effect within a subject. Moreover, the bioactive component may remain linked to a portion of the polymer or be released from the polymer. A "biobeneficial component" can be a substance that can be

4

combined with a polymer and provide a biological benefit within a subject without necessarily being released from the polymer.

Poly(ethylene-co-vinyl alcohol) (EVAL) is one example of a polymer that can be utilized as a hydrophobic component to fabricate the reservoir layer or the topcoat layer. EVAL can be used to make the optional primer layer as well. EVAL is a product of hydrolysis of ethylene-vinyl acetate copolymers and has the general formula  $-\text{[CH}_2-\text{CH}_2\text{]}_m-\text{[CH}_2-\text{CH(OH)}\text{]}_n-$ . EVAL may also include a terpolymer having up to about 5 molar % of units derived from styrene, propylene and other suitable unsaturated monomers. A brand of copolymer of ethylene and vinyl alcohol distributed commercially under the trade name EVAL by Aldrich Chemical Co. of Milwaukee, Wis., can be used.

Other examples of hydrophobic and hydrophilic components that can be used include polyacrylates, such as poly(butyl methacrylate), poly(ethyl methacrylate), and poly(ethyl methacrylate-co-butyl methacrylate), and fluorinated polymers and/or copolymers, such as poly(vinylidene fluoride) and poly(vinylidene fluoride-co-hexafluoro propene), poly(vinyl pyrrolidone), poly(hydroxyvalerate), poly(L-lactic acid), polycaprolactone, poly(lactide-co-glycolide), poly(hydroxybutyrate), poly(hydroxybutyrate-co-valerate), polydioxanone, polyorthoester, polyanhydride, poly(glycolic acid), poly(D,L-lactic acid), poly(glycolic acid-co-trimethylene carbonate), polyphosphoester, polyphosphoester urethane, poly(amino acids), cyanoacrylates, poly(trimethylene carbonate), poly(iminocarbonate), co-poly(ether-esters), polyalkylene oxalates, polyphosphazenes, biomolecules (such as fibrin, fibrinogen, cellulose, starch, collagen and hyaluronic acid), polyurethanes, silicones, polyesters, polyolefins, polyisobutylene and ethylene-alpha-olefin copolymers, vinyl halide polymers and copolymers (such as polyvinyl chloride), polyvinyl ethers (such as polyvinyl methyl ether), polyvinylidene chloride, polyacrylonitrile, polyvinyl ketones, polyvinyl aromatics (such as polystyrene), polyvinyl esters (such as polyvinyl acetate), copolymers of vinyl monomers with each other and olefins (such as ethylene-methyl methacrylate copolymers, acrylonitrile-styrene copolymers, ABS resins, and ethylene-vinyl acetate copolymers), polyamides (such as Nylon 66 and polycaprolactam), alkyd resins, polycarbonates, polyoxymethylenes, polyimides, polyethers, epoxy resins, polyurethanes, rayon, rayon-triacetate, cellulose, cellulose acetate, cellulose butyrate, cellulose acetate butyrate, cellophane, cellulose nitrate, cellulose propionate, cellulose ethers, and carboxymethyl cellulose.

Representative examples of some solvents suitable for making the stent coatings include N,N-dimethylacetamide (DMAC), N,N-dimethylformamide (DMF), tetrahydrofuran (THF), cyclohexanone, xylene, toluene, acetone, i-propanol, methyl ethyl ketone, propylene glycol monomethyl ether, methyl butyl ketone, ethyl acetate, n-butyl acetate, and dioxane. Some solvent mixtures can be used as well. Representative examples of the mixtures include:

- (1) DMAC and methanol (e.g., a 50:50 by mass mixture);
- (2) water, i-propanol, and DMAC (e.g., a 10:3:87 by mass mixture);
- (3) i-propanol and DMAC (e.g., 80:20, 50:50, or 20:80 by mass mixtures);
- (4) acetone and cyclohexanone (e.g., 80:20, 50:50, or 20:80 by mass mixtures);
- (5) acetone and xylene (e.g. a 50:50 by mass mixture);
- (6) acetone, FLUX REMOVER AMS, and xylene (e.g., a 10:50:40 by mass mixture); and

US 7,063,884 B2

5

(7) 1,1,2-trichloroethane and chloroform (e.g., a 80:20 by mass mixture).

FLUX REMOVER AMS is trade name of a solvent manufactured by Tech Spray, Inc. of Amarillo, Tex. comprising about 93.7% of a mixture of 3,3-dichloro-1,1,1,2,2-pentafluoropropane and 1,3-dichloro-1,1,2,2,3-pentafluoropropane, and the balance of methanol, with trace amounts of nitromethane. Those having ordinary skill in the art will select the solvent or a mixture of solvents suitable for a particular polymer being dissolved.

Following the formation of the stent coating comprising hydrophobic and hydrophilic polymers or components, the coating can be treated to enrich the surface with the hydrophilic polymer(s) or component(s). The coating can be dry, i.e., solvent free or wet, i.e., any amount of solvent during the treatment process. The stent coating referred to herein can be the reservoir layer, the topcoat layer, an outermost layer or a combination of any layers including the primer layer. As a result of promotion of the hydrophilic substance, a region of the coating layer on or about the outermost surface of the coating layer will have a higher amount, content or concentration of the hydrophilic component than the hydrophobic component. The region of the coating closer to the stent surface will have a higher amount, content or concentration of the hydrophilic component.

According to one method of the post-coating treatment, the coated stent can be exposed to the environment of a humidifying chamber. The length of such treatment can be between about 12 hours and 28 hours, for example, about 24 hours, at a temperature of about 40° C. to about 80° C., more narrowly, between about 45° C. and about 60° C., for example, about 50° C. and relative humidity of about 90% to about 100%. Any commercially available humidifying chamber can be used. As a result of the exposure of the stent to high humidity levels at elevated temperatures, water is expected to be deposited on the surface of the stent coating. Water will gradually extract the hydrophilic polymer to the coating surface leading to migration of the hydrophilic polymer and its blooming to the coating-air interface.

According to another method of the post-coating treatment, the coated stent can be physically placed on a film of a hydrogel, for example, a poly(vinyl alcohol) hydrogel, and gently rolled back and forth a number of times covering the entire circumference of the stent. For example, the coated stent can be rolled in the described fashion between 5 and 10 times, while a pressure of between about 1 atm and 3 atm is applied to the stent when it is being rolled. The physical contact between the film of the hydrogel and the stent coating can alter the coating-air interface, resulting in extraction of the hydrophilic polymer and its blooming to the coating-air interface.

According to yet another method of the post-coating treatment, the coated stent can be cooled or chilled at a temperature below ambient temperature. In some embodiments between about 4° C. and about -20° C. for a period of time between about 30 minutes and about 2 hours. Following the cooling process, the stent can be either exposed to ambient air for about 24 hours, or treated in the humidifying chamber as described above. This procedure is expected to lead to condensation of water on the surface of the coating, resulting in extraction of the hydrophilic polymer and its blooming to the coating-air interface.

Optionally, any combination of the three methods of the post-coating treatment described above can be used, if desired. As another option, following the post-coating treatment, the coated stent can be heated to a temperature which

6

is about equal to the glass transition temperature ( $T_g$ ) of the hydrophobic component of the coating.

In another embodiment, instead of a blend of a hydrophobic and hydrophilic polymer, an interpenetrating polymer network (IPN) can be used to make the outermost layer of the stent coating, the IPN includes at least one hydrophobic component and at least one hydrophilic component. For the purposes of the present invention, the definition of the IPN used by the International Union of Pure and Applied Chemistry (IUPAC) is adopted. The IUPAC describes the IPN as a polymer comprising two or more networks which are at least partially interlaced on a molecular scale, to form both chemical and physical bonds between the networks. The networks of an IPN cannot be separated unless chemical bonds are broken. In other words, an IPN structure represents two or more polymer networks that are partially chemically cross-linked and partially physically entangled. One example of an IPN that can be used is a surface hydrogel.

One example of a product that can be used for forming the IPN is a PEG-based unsaturated product, for example, pre-polymer of PEG-acrylate or PEG-methacrylate having a general formula  $\text{CH}_2=\text{CX}-\text{COO}-[\text{CH}_2-\text{CH}_2-\text{O}]_n-\text{H}$ , where X is hydrogen (acrylates) or methyl (methacrylates). The molecular weight of PEG-acrylate or methacrylate can be within a range of about 10,000 to 100,00 Daltons. PEG-acrylate or PEG-methacrylate prepolymer can be applied on the surface of the drug-polymer layer or topcoat layer and cured, for example, using a radical initiator which is activated by UV radiation (UV initiators), light (light initiators), or heat (thermal initiators). Examples of appropriate initiators include acetophenone, 2,2-dimethoxy-2-phenol-acetophenone (UV initiators), camproquinone, ethyl-4-N,N-dimethyl aminobenzoate (light initiators), and benzoyl peroxide (thermal initiator). As a result of the curing process, PEG-acrylate or PEG-methacrylate will partially cross-link and partially physically entangle with the polymer of the underlying drug-polymer layer thus forming the outermost coat layer which includes an IPN. PEG-acrylate or PEG-methacrylate is intended to broadly include poly(ethylene glycol)-diacrylate (PEG-diacrylate) and poly(ethylene glycol)-dimethacrylate (PEG-dimethacrylate). PEG-acrylate or PEG-methacrylate and PEG-diacrylate or PEG-dimethacrylate can be optionally terminated, for example, with stearic acid, to form PEG-acrylate-stearate or PEG-methacrylate-stearate, respectively.

Examples of other products that can be used for forming the IPN include such unsaturated reactive products as N-vinylpyrrolidone, heparin and its derivatives, hyaluronic acid and its derivatives, some hydrogel-forming products such as poly(butylene terephthalate-co-ethylene glycol) (PBT-PEG), and mixtures of any of these products with each other or with PEG-acrylate or PEG-methacrylate. A type of PBT-PEG polymers is also known under a trade name POLYACTIVE and is available from IsoTis Corp. of Holland.

After the IPN-based outermost coating has been formed, it can be subjected to a post-coating treatment to cause blooming or migration of the hydrophilic component of the IPN to the coating-air interface. For example, any method of the post-coating treatment described above, or any combination thereof, can be used.

One kind of an IPN is a hydrogel. If it is desirable to include a hydrogel in the outermost layer of the stent coating, PBT-PEG can be used as a hydrogel-forming product. PBT-PEG can be utilized for fabricating not only the outermost layer (e.g., the topcoat layer) of the coating but for making all other layers of the stent-coating (e.g., the primer

US 7,063,884 B2

7

layer or the drug-polymer layer) as well. In one embodiment, the stent coating can include only PBT-PEG and be free of any other polymers. The molecular weight of the PEG portion of the PBT-PEG polymer can be between about 300 and about 4,000 Daltons. In PBT-PEG polymer, the units derived from ethylene glycol ("the PEG units") can constitute between about 40 and about 90 molar % of the total PBT-PEG polymer. For example, the PEG units can constitute between about 55 and about 80 molar % of the total PBT-PEG polymer.

The active agent or a drug can include any substance capable of exerting a therapeutic or prophylactic effect in the practice of the present invention. The drug may include small molecule drugs, peptides, proteins, oligonucleotides, and the like. Examples of drugs include antiproliferative substances such as actinomycin D, or derivatives and analogs thereof. Synonyms of actinomycin D include dactinomycin, actinomycin IV, actinomycin I<sub>1</sub>, actinomycin X<sub>1</sub>, and actinomycin C<sub>1</sub>. The active agent can also fall under the genus of antineoplastic, anti-inflammatory, antiplatelet, anticoagulant, antifibrin, antithrombin, antimitotic, antibiotic, antiallergic and antioxidant substances. Examples of such antineoplastics and/or antimitotics include paclitaxel, docetaxel, methotrexate, azathioprine, vincristine, vinblastine, fluorouracil, doxorubicin, hydrochloride, and mitomycin. Examples of such antiplatelets, anticoagulants, antifibrin, and antithrombins include sodium heparin, low molecular weight heparins, heparinoids, hirudin, argatroban, forskolin, vapiprost, prostacyclin and prostacyclin analogs, dextran, D-phe-pro-arg-chloromethylketone (synthetic antithrombin), dipyridamole, glycoprotein IIb/IIIa platelet membrane receptor antagonist antibody, recombinant hirudin, and thrombin. Examples of such cytostatic or antiproliferative agents include angiostatin, angiotensin converting enzyme inhibitors such as captopril, cilazapril or lisinopril, calcium channel blockers (such as nifedipine), colchicine, fibroblast growth factor (FGF) antagonists, fish oil ( $\omega$ -3-fatty acid), histamine antagonists, lovastatin (an inhibitor of HMG-CoA reductase, a cholesterol lowering drug), monoclonal antibodies (such as those specific for Platelet-Derived Growth Factor (PDGF) receptors), nitroprusside, phosphodiesterase inhibitors, prostaglandin inhibitors, suramin, serotonin blockers, steroids, thioprotease inhibitors, triazolopyrimidine (a PDGF antagonist), and nitric oxide. An example of an antiallergic agent is permirrolast potassium.

Other therapeutic substances or agents which may be appropriate include alpha-interferon; genetically engineered epithelial cells; rapamycin and structural derivatives or functional analogs thereof, such as 40-O-(2-hydroxy)ethyl-rapamycin (known by the trade name of everolimus available from Novartis), 40-O-(3-hydroxy)propyl-rapamycin, 40-O-[2-(2-hydroxy)ethoxy]ethyl-rapamycin, and 40-O-tetrazole-rapamycin, tacrolimus, and dexamethasone.

The coatings and methods of the present invention have been described with reference to a stent, such as a balloon expandable or self-expandable stent. The use of the coating is not limited to stents, however, and the coating can also be used with a variety of other medical devices. Examples of the implantable medical device, that can be used in conjunction with the embodiments of this invention include stent-grafts, grafts (e.g., aortic grafts), artificial heart valves, cerebrospinal fluid shunts, pacemaker electrodes, axiis coronary shunts and endocardial leads (e.g., FINELINE and ENDOTAK, available from Guidant Corporation). The underlying structure of the device can be of virtually any design. The device can be made of a metallic material or an alloy such as, but not limited to, cobalt-chromium alloys

8

(e.g., ELGILOY), stainless steel (316L), "MP35N," "MP20N," ELASTINITE (Nitinol), tantalum, tantalum-based alloys, nickel-titanium alloy, platinum, platinum-based alloys such as, e.g., platinum-iridium alloy, iridium, gold, magnesium, titanium, titanium-based alloys, zirconium-based alloys, or combinations thereof. Devices made from bioabsorbable or biostable polymers can also be used with the embodiments of the present invention.

"MP35N" and "MP20N" are trade names for alloys of cobalt, nickel, chromium and molybdenum available from Standard Press Steel Co. of Jenkintown, Pa. "MP35N" consists of 35% cobalt, 35% nickel, 20% chromium, and 10% molybdenum. "MP20N" consists of 50% cobalt, 20% nickel, 20% chromium, and 10% molybdenum.

Embodiments of the present invention can be further illustrated by the following set forth examples.

#### EXAMPLE 1

A first composition can be prepared by mixing the following components:

(a) between about 1.0 mass % and about 15 mass %, for example, about 2.0 mass % EVAL; and

(b) the balance, DMAC solvent.

The first composition can be applied onto the surface of a bare 13 mm TETRA stent (available from Guidant Corporation) by spraying and dried to form a primer layer. A spray coater can be used having a 0.014 fan nozzle maintained at about 60° C. with a feed pressure of about 0.2 atm (about 3 psi) and an atomization pressure of about 1.3 atm (about 20 psi). About 70  $\mu$ g of the wet coating can be applied. The primer can be baked at about 140° C. for about 2 hours, yielding a dry primer layer.

A second composition can be prepared by mixing the following components:

(a) between about 1.0 mass % and about 15 mass %, for example, about 2.0 mass % EVAL;

(b) between about 0.05 mass % and about 2.0 mass %, for example, about 1.0 mass % everolimus; and

(c) the balance, DMAC solvent.

The second composition can be applied onto the dried primer layer to form the reservoir layer, using the same spraying technique and equipment used for applying the primer layer. About 400  $\mu$ g of the wet coating can be applied, followed by drying, e.g., by baking as described above.

A third composition can be prepared by mixing the following components:

(a) between about 1.0 mass % and about 15 mass %, for example, about 2.0 mass % EVAL;

(b) between about 0.5 mass % and about 5.0 mass %, for example, about 1.0 mass % poly(ethylene glycol) having molecular weight of about 17,500; and

(c) the balance, a solvent mixture comprising DMAC and ethanol (EtOH) in a mass ratio DMAC:EtOH of about 4:1.

The third composition can be applied onto the dried reservoir layer to form a topcoat layer, using the same spraying technique and equipment used for applying the primer layer and the reservoir layer. About 200  $\mu$ g of the wet coating can be applied, followed by drying, e.g., by baking as described above.

The coated stent can be placed in a humidifying chamber for about 24 hours, at a temperature of about 50° C. and relative humidity of about 100%, followed by removing the stent from the humidifying chamber and drying.

US 7,063,884 B2

9

## EXAMPLE 2

The stent can be coated as described in Example 1, except when preparing the composition for fabricating the topcoat layer, instead of poly(ethylene glycol) having molecular weight of about 17,500, poly(ethylene glycol)-stearate having molecular weight of about 4,000 can be used.

The coated stent can be treated in the humidifying chamber as described in Example 1.

## EXAMPLE 3

The stent can be coated as described in Example 1. The coated stent can be placed in a refrigerating unit and exposed to a temperature of about -10° C. for about 1 hour. Following the cooling process, the stent can be dried in the ambient atmosphere for about 24 hours.

## EXAMPLE 4

A first composition was prepared by mixing the following components:

- (a) about 2.0 mass % PBT-PEG; and
- (b) the balance, a solvent blend, the blend comprising 1,1,2-trichloroethane and chloroform in a mass ratio between 1,1,2-trichloroethane and chloroform of about 4:1.

The brand of PBT-PEG that was used had about 45 molar % units derived from PBT and about 55 molar % units derived from PEG. The molecular weight of the PEG units was about 300 Daltons. The first composition was applied onto the surface of a bare 13 mm PENTA stent (available from Guidant Corporation) by spraying and dried to form a primer layer. The primer was baked at about 140° C. for about 1 hour, yielding a dry primer layer having solids content of about 100 µg. "Solids" means the amount of the dry residue deposited on the stent after all volatile organic compounds (e.g., the solvent) have been removed.

A second composition was prepared by mixing the following components:

- (a) about 2 mass % PBT-PEG;
- (b) about 2 mass % everolimus; and
- (c) the balance, the blend of 1,1,2-trichloroethane and chloroform described above.

The same brand of PBT-PEG as that utilized for making the primer layer was used. The second composition was applied onto the dried primer layer to form the reservoir layer. The second composition was baked at about 50° C. for about 1 hour, yielding a dry reservoir layer having solids content of about 300 µg.

A third composition was prepared by mixing the following components:

- (a) about 2.0 mass % PBT-PEG having about 20 molar % units derived from PBT and about 80 molar % units derived from PEG. The molecular weight of the PEG units was about 4,000 Daltons; and
- (b) the balance, the blend of 1,1,2-trichloroethane and chloroform described above.

The third composition was applied onto the dried reservoir layer to form a topcoat layer. The third composition was baked at about 50° C. for about 2 hours, yielding a dry topcoat layer having solids content of about 100 µg.

10

## EXAMPLE 5

A stent was coated with a primer layer and a reservoir layer as described in Example 4. A composition was prepared, comprising:

- (a) about 1.0 mass % PBT-PEG having about 45 molar % units derived from PBT and about 55 molar % units derived from PEG. The molecular weight of the PEG units was about 300 Daltons;
- (b) about 1.0 mass % PBT-PEG having about 20 molar % units derived from PBT and about 80 molar % units derived from PEG. The molecular weight of the PEG units was about 4,000 Daltons; and
- (c) the balance, the blend of 1,1,2-trichloroethane and chloroform described above.

The composition was applied onto the dried reservoir layer and dried to form a topcoat layer, as described in Example 4. The topcoat layer had solids content of about 100 µg.

## EXAMPLE 6

A stent was coated with a primer layer and a reservoir layer as described in Example 4. A composition was prepared, comprising:

- (a) about 1.0 mass % PBT-PEG having about 45 molar % units derived from PBT and about 55 molar % units derived from PEG. The molecular weight of the PEG units was about 300 Daltons;
- (b) about 1.0 mass % PBT-PEG having about 40 molar % units derived from PBT and about 60 molar % units derived from PEG. The molecular weight of the PEG units was about 1,000 Daltons; and
- (c) the balance, 1,4-dioxane solvent.

The composition was applied onto the dried reservoir layer and dried to form a topcoat layer, as described in Example 4. The topcoat layer had solids content of about 100 µg.

## EXAMPLE 7

A stent was coated with a primer layer described in Example 4. A first composition was prepared by mixing the following components:

- (a) about 2 mass % PBT-PEG;
- (b) about 2 mass % paclitaxel; and
- (c) the balance, the blend of 1,1,2-trichloroethane and chloroform described above.

The same brand of PBT-PEG as that utilized for making the primer layer was used. The first composition was applied onto the dried primer layer and dried to form a reservoir layer, as described in Example 4. The reservoir layer had solids content of about 300 µg.

A second composition was prepared by mixing the following components:

- (a) about 1.5 mass % PBT-PEG having about 45 molar % units derived from PBT and about 55 molar % units derived from PEG. The molecular weight of the PEG units was about 300 Daltons;
- (b) about 0.5 mass % PBT-PEG having about 20 molar % units derived from PBT and about 80 molar % units derived from PEG. The molecular weight of the PEG units was about 4,000 Daltons; and
- (c) the balance, the blend of 1,1,2-trichloroethane and chloroform described above.

The composition was applied onto the dried reservoir layer and dried to form a topcoat layer, as described in Example 4. The topcoat layer had solids content of about 100 µg.

US 7,063,884 B2

## 11

## EXAMPLE 8

A stent was coated with a primer layer and a reservoir layer as described in Example 7. A composition was prepared, comprising:

(a) about mass 1.0% of PBT-PEG having about 45 molar % units derived from PBT and about 55 molar % units derived from PEG. The molecular weight of the PEG units was about 300 Daltons; and

(b) 1.0 about mass % PBT-PEG having about 20 molar % units derived from PBT and about 80 molar % units derived from PEG. The molecular weight of the PEG units was about 4,000 Daltons;

(c) the balance, the blend of 1,1,2-trichloroethane and chloroform described above.

The composition was applied onto the dried reservoir layer and dried to form a topcoat layer, as described in Example 7. The topcoat layer had solids content of about 100 µg.

## EXAMPLE 9

A 12 mm VISION stent (available from Guidant Corp.) was coated with a primer layer described in Example 4. A first composition was prepared by mixing the following components:

(a) about 2 mass % everolimus; and

## 12

(b) the balance a the blend of acetone and xylene in a mass ratio between acetone and xylene of about 2:3.

The first composition was applied onto the dried primer layer to form the reservoir layer. The first composition was baked at about 50° C. for about 1 hour, yielding a dry reservoir layer having solids content of about 200 µg.

A second composition was prepared, comprising:

(a) about 2.0 mass % of PBT-PEG having about 45 molar % units derived from PBT and about 55 molar % units derived from PEG. The molecular weight of the PEG units was about 300 Daltons; and

(b) the balance, the blend of 1,1,2-trichloroethane and chloroform described above.

The second composition was applied onto the dried reservoir layer and dried to form a topcoat layer, as described in Example 4.

The coating compositions discussed in Examples 1–9 are summarized in Table 1.

While particular embodiments of the present invention have been shown and described, it will be obvious to those skilled in the art that changes and modifications can be made without departing from this invention in its broader aspects. Therefore, the appended claims are to encompass within their scope all such changes and modifications as fall within the true spirit and scope of this invention.

TABLE 1

Stent Coatings of Examples 1–9				
Example	Primer	Reservoir		Topcoat
	Polymer	Polymer	Drug	Polymer
1	EVAL	EVAL	everolimus	1. EVAL 2. PEG (EVAL:PEG ratio is 2:1)
2	EVAL	EVAL	everolimus	1. EVAL 2. PEG-stearate (EVAL:PEG-stearate ratio is 2:1)
3	EVAL	EVAL	everolimus	1. EVAL 2. PEG (EVAL:PEG ratio is 2:1)
4	PBT-PEG PBT - 45 mol. % PEG - 55 mol. % PEG's MW = 300	PBT-PEG PBT - 45 mol. % PEG - 55 mol. % PEG's MW = 300	everolimus	PBT-PEG PBT - 20 mol. %; PEG - 80 mol. % PEG's MW = 4,000
5	PBT-PEG PBT - 45 mol. % PEG - 55 mol. % PEG's MW = 300	PBT-PEG PBT - 45 mol. % PEG - 55 mol. % PEG's MW = 300	everolimus	(1) PBT-PEG PBT - 45 mol. %; PEG - 55 mol. % PEG's MW = 300 (2) PBT-PEG PBT - 20 mol. %; PEG - 80 mol. % PEG's MW = 4,000 Ratio (1) PBT-PEG:(2) PBT-PEG = 1:1
6	PBT-PEG PBT - 45 mol. % PEG - 55 mol. % PEG's MW = 300	PBT-PEG PBT - 45 mol. % PEG - 55 mol. % PEG's MW = 300	everolimus	(1) PBT-PEG PBT - 45 mol. %; PEG - 55 mol. % PEG's MW = 300 (2) PBT-PEG PBT - 40 mol. %; PEG - 60 mol. % PEG's MW = 1,000 Ratio (1) PBT-PEG:(2) PBT-PEG = 1:1
7	PBT-PEG PBT - 45 mol. % PEG - 55 mol. % PEG's MW = 300	PBT-PEG PBT - 45 mol. % PEG - 55 mol. % PEG's MW = 300	Paclitaxel	(1) PBT-PEG PBT - 45 mol. %; PEG - 55 mol. % PEG's MW = 300 (2) PBT-PEG PBT - 20 mol. %; PEG - 80 mol. % PEG's MW = 4,000 Ratio (1) PBT-PEG:(2) PBT-PEG = 3:1
8	PBT-PEG PBT - 45 mol. % PEG - 55 mol. % PEG's MW = 300	PBT-PEG PBT - 45 mol. % PEG - 55 mol. % PEG's MW = 300	Paclitaxel	(1) PBT-PEG PBT - 45 mol. %; PEG - 55 mol. % PEG's MW = 300 (2) PBT-PEG PBT - 20 mol. %; PEG - 80 mol. % PEG's MW = 4,000 Ratio (1) PBT-PEG:(2) PBT-PEG = 1:1



US 7,063,884 B2

13

14

TABLE 1-continued

Stent Coatings of Examples 1-9				
Primer		Reservoir		Topcoat
Example	Polymer	Polymer	Drug	Polymer
9	PBT-PEG PBT - 45 mol. % PEG - 55 mol. % PEG's MW*) = 300	N/A	everolimus	PBT-PEG PBT - 45 mol. % PEG - 55 mol. % PEG's MW*) = 300

\*)MW is an abbreviation for "molecular weight"

What is claimed is:

1. A stent comprising a coating layer, the coating layer having a hydrophobic component and a hydrophilic component, wherein a region of the coating layer on or about the outermost surface of the coating layer has a higher content or concentration of the hydrophilic component than the hydrophobic component and wherein the hydrophilic component has a solubility parameter higher than about 8.5 (cal/cm<sup>3</sup>)<sup>1/2</sup>.

2. The stent of claim 1, wherein the hydrophobic and hydrophilic components are blended in the coating layer.

3. The stent of claim 1, wherein the hydrophobic and hydrophilic components are bonded in the coating layer.

4. The stent of claim 1, wherein the hydrophobic and hydrophilic components are an interpenetrating polymer network.

5. The stent of claim 1, wherein the solubility parameter is higher than about 9.0 (cal/cm<sup>3</sup>)<sup>1/2</sup>.

6. The stent of claim 1, wherein the solubility parameter is higher than about 9.5 (cal/cm<sup>3</sup>)<sup>1/2</sup>.

7. The stent of claim 1, wherein the solubility parameter is higher than about 10.0 (cal/cm<sup>3</sup>)<sup>1/2</sup>.

8. The stent of claim 1, wherein the solubility parameter is higher than about 10.5 (cal/cm<sup>3</sup>)<sup>1/2</sup>.

9. The stent of claim 1, wherein the solubility parameter is higher than about 11.0 (cal/cm<sup>3</sup>)<sup>1/2</sup>.

10. The stent of claim 1, wherein the solubility parameter is higher than about 11.5 (cal/cm<sup>3</sup>)<sup>1/2</sup>.

11. The stent of claim 1, wherein the hydrophobic component has a solubility parameter less than about 11.5 (cal/cm<sup>3</sup>)<sup>1/2</sup>.

12. The stent of claim 1, wherein the coating layer includes one or a combination of a primer layer, a reservoir layer including a drug and a topcoat layer.

13. The stent of claim 1, wherein the coating layer is the outermost layer of a coating construct.

14. The stent of claim 1, wherein the ratio of the hydrophilic component to the hydrophobic component is between about 1:100 and about 1:9.

\* \* \* \* \*